Dysfunction of cellular analgesic control in neuropathic pain

Neuropathic pain in small-fiber neuropathy was traditionally considered a consequence of injury to nociceptors and sensitization. An alternative view has also been put forward: there may be a loss of the neuronal analgesic control system, paralleling the sensitized nociceptive system and leading to neuropathic pain. This process may involve adenosine, a cellular analgesic effector that is hydrolyzed from adenine monophosphate (AMP) by prostatic acid phosphatase (PAP), a glycoprotein synthesized by the prostate gland. PAP is thought to have ectonucleotidase activity, which is critical for responding to pathophysiological cellular homeostasis. In this way, PAP downregulation may lead to an imbalance in the AMP/adenosine ratio, causing a dysfunction in neuronal analgesic control. Indeed, recent studies have found that PAP, typically used to diagnose prostate cancer, has a molecular identity similar to thiamine monophosphatase, which is widely used for labeling nociceptive dorsal root ganglia (DRG) neurons. It is therefore reasonable to link PAP neuropathology and disorders of the neuronal analgesic system in the development of neuropathic pain.

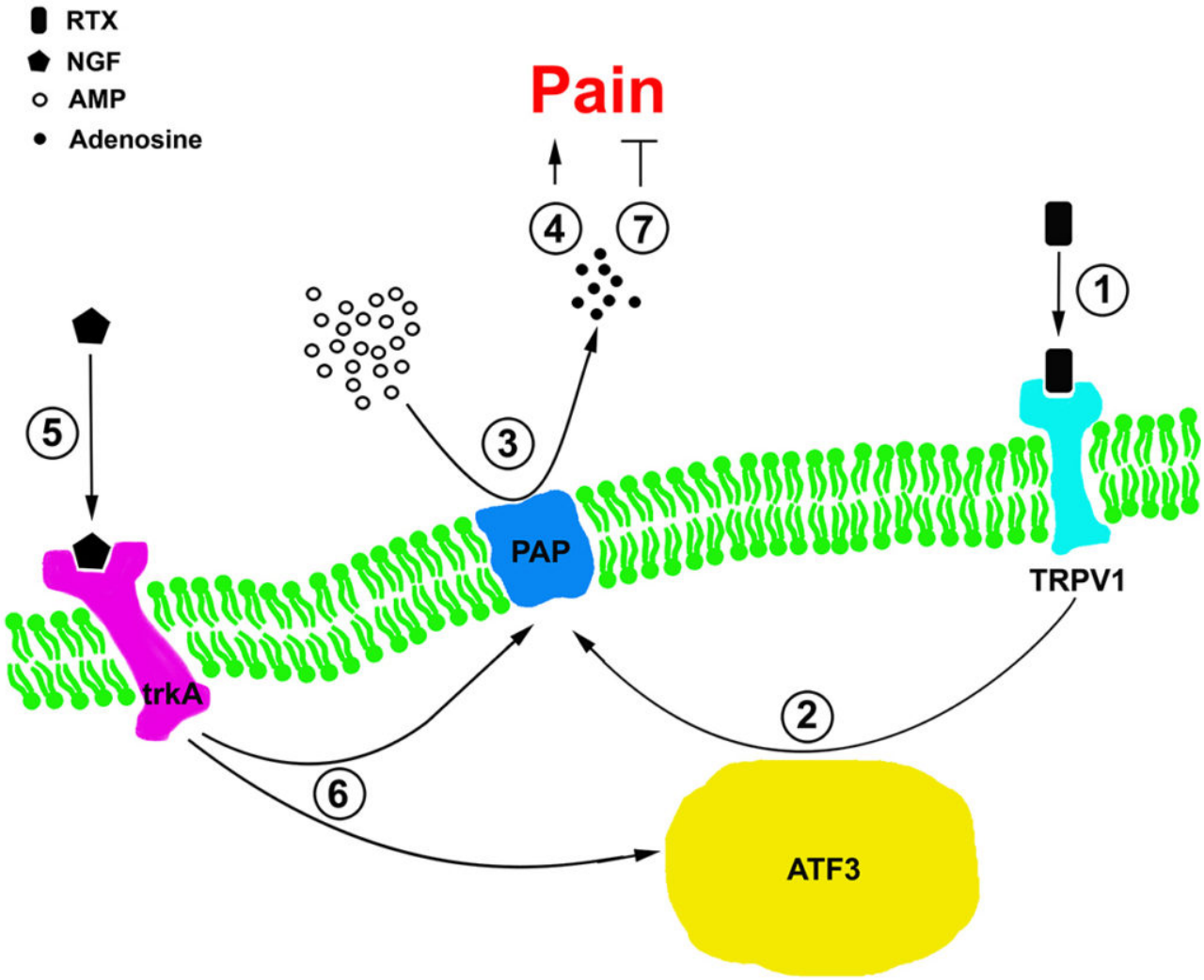

Fig. 1. Diagram of prostatic acid phosphatase (PAP) pathology that modulates pain perception in small fiber neuropathy. This diagram illustrates the PAP pathology mediating pain development follows a NGF-trkA-dependent manner, as described in the following steps: (1) The transient receptor potential vanilloid subtype 1 (TRPV1) was sensitized by resiniferatoxin (RTX), an ultrapotent of capsaicin. (2) RTX then induces activating transcription factor-3 (ATF3) upregulation on PAP(+) neurons, indicating the PAP pathology. (3) The PAP pathology reduces the AMP hydrolysis. (4) This reduction evokes pain perception because of the decrease in the adenosine analgesic effect. (5) Nerve growth factor (NGF) binds to high-affinity NGF receptor (trkA) and (6) reverses the induction of the ATF3 and PAP pathology. (7) This recovers the PAP-mediated analgesic effect by returning the ability of AMP hydrolysis.

The peripheral targets of nociceptive DRG neurons in the skin are intraepidermal nerve fibers (IENFs), while IENF degeneration is a main pathological characteristic of small fiber neuropathy. The degree of IENF degeneration in small fiber neuropathy is associated with injury to neuronal soma which can be labeled by activating transcription factor-3 (ATF3). Our study found that PAP was expressed by small- to medium-sized nociceptive DRG neurons (25th–75th percentile: 17.1–23.7 μm) and that in a pure small fiber neuropathy model these PAP-expressing nociceptive DRG neurons were decreased in number and around 30% were labeled by ATF3, indicating they had undergone degeneration. The degree of PAP neuropathology correlated with the degree of mechanical allodynia, a symptom of mechanical hypersensitivity characteristic of small fiber neuropathy.

Nociceptive DRG neurons are regulated functionally and morphologically by different neurotrophic factors and cognate receptors. For example, nerve growth factor (NGF) is trophic to nociceptive DRG neurons and modulates neuropathic pain through its high-affinity receptor, trkA. However, NGF is a macromolecular protein and exogenous NGF frequently induces the immune response. In addition, from an economic perspective, commercial purified NGF protein is expensive. Hanaoka et al (1992) and Saita et al (1995) found that a small molecular chemical compound, 4-methylcatechol (4MC), could enhance the synthesis of NGF. In addition, our group demonstrated that 4MC promoted IENF regeneration and reversed neuropathic pain. Specifically, we found that 4MC was effective in reversing PAP pathology and mechanical allodynia due to the high coexpression of PAP and TrkA. Administering purified NGF protein with an intraperitoneal injection showed similar results to administering 4MC, and the effect of 4MC was eliminated by NGF neutralization. It is clear that 4MC not only promotes nerve regeneration but also facilitates the recovery of irritated and/or injured small-diameter neuronal soma. Our current findings suggest that damage to neuronal soma underlies the irritation and/or injury coincident with the metabolic imbalance of extracellular nucleotides, which results in the loss of the analgesic effect of PAP. Our findings also are the first to document an intervention against PAP pathology and NGF-trkA signaling, which mediates neuropathic pain. We suggest that restoring the analgesic ligand, and thereby maintaining static levels of adenosine and normal PAP ectonucleotidase activity in the neuronal

soma, may offer a new direction for research into painful neuropathy.

In summary, ATF3 seems to be an upstream molecule that initiates the loss of the analgesic effect of PAP, while NGF-trkA signaling restores the analgesic effect of PAP in a trkA-dependent manner (Fig. 1).

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